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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,438	07/03/2001	Katsuhiko Mikoshiba	4853.0076.00000	8360

22852 7590 01/13/2003

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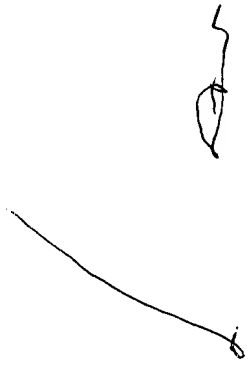
EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 01/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.



Office Action Summary	Application No.	Applicant(s)	
	09/897,438	MIKOSHIBA ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8, 10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: The brief Description of the drawings should be amended to reflect the views, i.e., Fig. 1A-1D, Fig. 2A-2G, Fig. 3A-3F, Fig. 4A-4C, Fig. 5A-5D, Fig. 6A-6F.

Appropriate correction is required.

Election/Restriction

2. Applicant's election of Group II, claims 4-8 and 10-11 in part in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-3 and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claim Objections

4. Claims 4, 6-8 and 10-11 are objected to because of the following informalities: The claims are objected to as depending in part from a withdrawn, non-elected invention. Appropriate correction is required.

5. Claims 10-11 are objected to as reciting an improper Markush Group. M.P.E.P. 803.02 states that:

"Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine

that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

In particular, claims 10-11 are drawn to two independent and distinct inventions as set forth in the restriction requirement. The elected invention is of polynucleotides and the claims are examined to the extent thereto.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for polynucleotides of alternative sequence as claimed including deletion, insertion, substitution and degenerate sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to

this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. Thus, these references exemplify the importance of conserved structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted and that variations in sequence may effect such structure and immunological recognition.

Instant specification discloses a CR-50 epitope designated as SEQ ID NO:2, residues 230-346 of Reelin protein, see in particular p. 4, lines 11-18. However, the claims are drawn generically to polynucleotides encoding a CR-50 epitope region polypeptide of Reelin protein which comprises a CR-50 antibody recognition site but comprises neither a F-spondin domain nor a repeat site, and to polynucleotides encoding a polypeptide comprising SEQ ID NO:2 and deletion substitution or addition

mutations of SEQ ID NO:2 as presumably recited in claim 4. The claims are also drawn to polynucleotides of SEQ ID NO:1, to deletion, insertion and substitution mutations as well as to degenerate nucleotide sequences. Thus, the claims are directed to polynucleotides encoding peptides with greater than single amino acid substitutions, deletions and insertions and to partial peptide fragments which bind CR-50 antibody. Yet the specification fails to teach alternative sequences other than SEQ ID NO:2 encoded by SEQ ID NO:1 and degenerate sequences thereof, capable of binding CR-50 antibody that corresponds to the claim recitations. There is no disclosure of those residues which may be replaced, modified, inserted or deleted without abrogating the disclosed immunological reactivity. Moreover, as pertinent in claims 10-11, the specification fails to teach such suitable compositions for stimulating the assembly of Reelin protein molecules or for providing a pharmaceutical for diagnosis or treatment of diseases resulting from abnormally positioned neurons. At most the specification merely recognizes an eptiopic region which binds CR-50 antibody and which spontaneously forms a regular homopolymer via electrostatic interaction as disclosed at p. 4, lines 11-18. Furthermore, Reelin mutants are only recognized in mice and the model system is pertinent only to the Reelin phenotype which does not approximate all recognized abnormally positioned neurons but only those recognized as aberrantly positioned in Reelin animals, see for example Curran et al., Br. Res. Br. Res. Reviews, 26(2-3):285-94, May 1998.

The specification does not enable the broad scope of the claims that encompass a multitude of analogs or equivalents because the specification does not teach which

residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke immune responses or to provide for the required effects. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not expect functional conservation or immunological recognition among homologous sequences. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The artisan recognizes that such structure is critical to antibody binding. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed by the claims, one skilled in the art would be forced into undue experimentation in order to determine those peptides which correlate to the recitations of the claims, i.e., to define those residues capable of CR-50 monoclonal antibody binding, stimulating the assembly of Reelin proteins or diagnosing or treating diseases associated with abnormally positioned neruons. Further the artisan would be required to confirm the peptides utility in the process of making and using a polypeptide capable

of stimulating an antibody capable of binding reelin products, thus inhibiting Reelin function, see in particular Utsunomiya-Tate N., et al., PNAS, 97(17):9729-34, Aug. 15, 2000. Therefore, the enablement provided by the specification, in view of the skill in the art, is not commensurate in scope with the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 6-8 and 10-11 are indefinite as the claims depend upon withdrawn base claims and thus the metes and bounds are indefinite to the artisan. The claims should be rewritten so as to incorporate the subject matter to which the claims intend to be drawn.

Claim 5 is indefinite to the artisan as it recites in element (c) a polynucleotide comprising a degenerate nucleotide sequences of (a) or (b) where (a) and (b) are drawn to polynucleotides related to SEQ ID NO:1. While the artisan recognized degenerate nucleic acid sequences with respect to an amino acid sequence, the artisan fails to recognize a degenerate of a polynucleic acid sequence. Degeneracy is recognized with respect to the Genetic code wherein multiple nucleic acids encode a particular amino acid. The claim should be rewritten with respect to the amino acid sequence or to specify the relevant nucleic acids claimed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 4-8 and 10-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Curran et al., US 6,323,177 filed 6-16-1999, issued 11-27-01.

The claims have been interpreted as being drawn to the polynucleoitde encoding the polypeptide of withdrawn claim 3. Curran et al., teach Reelin polypeptide sharing 100% similarity with instant SEQ ID NO:2 and polynucleotides encoding the Reelin gene, see in particular 6,323,177, SEQ ID NO:3, residues 970-1320 sharing 100% similarity with instant SEQ ID NO:1, residues 1-351 and encoding SEQ ID NO:2, residues 1-117, see also attached alignment. The '177 patent further teaches isolated

nucleic acids inclusive of various insertion, deletion and addition mutants, as well as fragments thereof encoding particular polypeptides. These mutants include N'- and C'-terminal deletions as recited in column 20, lines 4-14 and column 22, line 48-column 23, line 7. The polypeptides are produced via vector constructs and host cells including fusion proteins as disclosed at columns 9-20 and columns 19-20 in particular. Thus, the patent recognizes polynucleotides encoding SEQ ID NO:2 as claimed in claim 4, polynucleotides of SEQ ID NO:1, as in claim 5, expression vectors, host cells and methods of producing the polypeptide as in claims 6-8. The patent discloses compositions comprising such polynucleotides for stimulating assembly or production of Reelin protein via recombinant DNA technology as in claim 10 and further include such for use in pharmaceutical interventions for example as an antisense nucleic acid treatment, disclosed in column 14, lines 14-30, for viral vector therapy, column 15-17 and for methods of treatment, column 24, lines 14-41, for neuronal migration defects, including those that result in cortical displasia and epilepsy. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

12. No claims are allowed.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is

(703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
January 7, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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